

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/078413 A1

- (51) International Patent Classification⁷: C07D 277/68, A61K 31/425, A61P 25/00
- (21) International Application Number: PCT/EP03/50063
- (22) International Filing Date: 17 March 2003 (17.03.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
02076481.7 18 March 2002 (18.03.2002) EP
- (71) Applicant (for all designated States except US): SOLVAY PHARMACEUTICALS B.V. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): LANGE, Josephus, H., M. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). KRUSE, Cornelis, G. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). HERREMANS, Arnoldus, H., J. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). VAN STUIVENBERG, Herman, H. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). DIJKSMAN, Jessica, A., R. [NL/NL];
- C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). MC-CREARY, Andrew, C. [GB/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).
- (74) Agent: VERHAGE, Marinus; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THIAZOLE DERIVATIVES HAVING CB₁-ANTAGONISTIC, AGONISTIC OR PARTIAL AGONISTIC ACTIVITY



(57) Abstract: The present invention relates to a group of thiazole derivatives which are potent antagonists, agonists or partial agonists of the cannabinoid CB₁-receptor. The compounds have the general formula (I) wherein R and R₁-R₄ have the meanings given in the specification.

WO 03/078413 A1

Thiazole derivatives having CB₁-antagonistic, agonistic or partial agonistic activity

The present invention relates to a group of thiazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned thiazole derivatives are potent cannabinoid (CB₁) receptor antagonists, CB₁ receptor agonists or CB₁ receptor partial agonists, with utility for the treatment of psychiatric and neurological disorders and other diseases involving cannabinoid CB₁ neurotransmission.

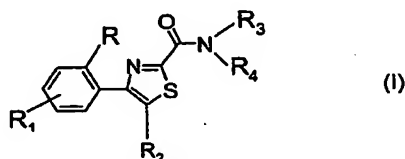
10

4,5-Diarylthiazole derivatives have been described in EP 388909 and EP 377457 as 5-lipoxygenase inhibitors for the treatment of thrombosis, hypertension, allergy and inflammation. The exemplified structures therein all contain two phenyl rings which are p-substituted with a methoxy, fluoro, methylthio or methylsulfinyl group. WO 9603392 describes sulfonylaryl-arylthiazoles for inflammation and pain, arthritis or fever as inflammation-associated disorders. JP 05345772 relates to 4,5-diarylthiazoles as acetyl cholinesterase inhibitors, and JP 04154773 describes 4,5-diarylthiazoles having analgesic, antiinflammatory and antipyretic action.

15

It has now surprisingly been found that the 4,5-diarylthiazole derivatives of the formula (I), pro-drugs thereof and salts thereof

20



25 wherein

- R represents a hydrogen atom or a substituent X from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl(C₁₋₃)sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl(C₁₋₃) aminosulfonyl, branched or unbranched monoalkyl(C₁₋₃)-aminosulfonyl and acetyl,

30

- R₁ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,

35

- R₂ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning or R₂ represents naphthyl,

- 5 - R_3 represents a hydrogen atom or a branched or unbranched C_{1-10} alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched C_{1-3} -alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, branched or unbranched (C_{1-3})-alkylsulfonyl, dimethylsulfamido, branched or unbranched C_{1-3} -alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_3 represents a pyridyl or thienyl group,
- 10 - R_4 represents branched or unbranched C_{1-10} alkyl or cycloalkyl-alkyl group, branched or unbranched C_{1-10} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, branched or unbranched C_{3-10} alkenyl, C_{5-8} cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

15 R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

20 - R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom,

25 atom,

30 atom,

are potent antagonists, agonists or partial agonists of the cannabinoid CB_1 receptor.

- 35 A pro-drug is an inactive compound, which when absorbed is converted into an active form (Medicinal Chemistry: Principles and Practice, 1994, ISBN 0-85186-494-5, Ed.: F. D. King, p. 216).

- 40 Due to the potent CB_1 receptor activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle

spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, cranio-cerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

10

The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB₁ receptor is stably transfected in conjunction with [³H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [³H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

15

20

The cannabinoid CB₁ receptor antagonistic, agonistic or partial agonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB₁ receptor-mediated response can be antagonised by CB₁ receptor antagonists or partial agonists such as the compounds of the invention.

25

30

Cannabinoid receptor agonistic or partial agonistic activity of compounds of the invention can be determined according to published methods, such as assessment of in vivo cannabimimetic effects (Wiley, J. L. et al., *J. Pharmacol. Exp. Ther.* **2001**, 296, 1013).

35

Cannabinoid receptor antagonists may behave as inverse agonists (Landsman, R. S. et al., *Eur. J. Pharmacol.* **1997**, 334, R1-R2).

The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I).

40

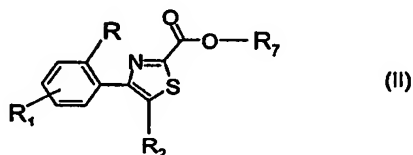
The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

A suitable synthesis for the compounds according to the present invention is the following:

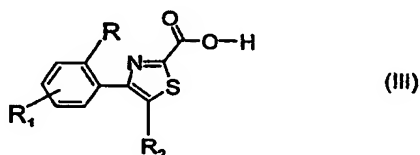
5 Synthesis route A

Step 1 of route A

Ester hydrolysis of a compound having formula (II) wherein R₇ represents a branched or unbranched alkyl group (C₁₋₄) or benzyl group.



This reaction gives a compound having formula (III)



wherein R, R₁ and R₂ have the meanings as described hereinabove.

- 15 The compounds of the invention having formula (II), wherein R₇ represents a branched or unbranched alkyl group (C₁₋₄) or benzyl group can be obtained according to methods known, for example:

- 20 a) Organic Reactions, Vol. VI, (1951), p. 367-409, Ed. R. Adams, John Wiley and Sons Inc., New York
 b) J. S. Carter et al., *Bioorg. Med. Chem. Lett.* (1999), 9, 1167-1170
 c) T. T. Sakai et al., *Bioorg. Med. Chem.* (1999), 7, 1559-1566
 d) A. Tanaka et al., *J. Med. Chem.* (1994), 37, 1189-1199
 e) J. J. Talley et al., WO 9603392: Chem. Abstr. 125, 33628
 25 f) V. Cecchetti et al., *Bioorg. Med. Chem.* (1994), 2, 799-806

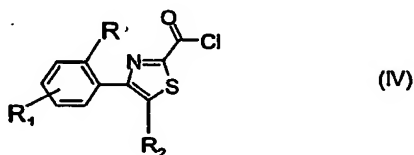
Step 2 of route A

- 30 Reaction of a compound having formula (III) with a compound having formula R₃R₄NH wherein R₃ and R₄ have the meanings as described hereinabove *v/a* activating and coupling methods such as formation of an active ester, or in the presence of a so-called coupling reagent, such as for example, DCC, HBTU, BOP,

- CIP (2-chloro-1,3-dimethylimidazolinium hexafluorophosphate), PyAOP (7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) and the like. (For more information on activating and coupling methods see a) M. Bodanszky, A. Bodanszky: *The Practice of Peptide Synthesis*, Springer-Verlag, New York, 1994; ISBN: 0-387-57505-7; b) K. Akaji et al., *Tetrahedron Lett.* (1994), 35, 3315-3318; c) F. Albericio et al., *Tetrahedron Lett.* (1997), 38, 4853-4856).

This reaction gives a desired thiazole derivative having formula (I).

- 10 Alternatively, a compound having formula (III) is reacted with a so-called halogenating agent such as for example thionyl chloride (SOCl_2). This reaction gives the corresponding carbonyl chloride (IV).



- 15 Reaction of a compound having formula (IV) with a compound having formula $\text{R}_3\text{R}_4\text{NH}$ wherein R_3 and R_4 have the meanings as described hereinabove gives a thiazole derivative having formula (I). This reaction is preferably carried out in the presence of an organic base such as for example diisopropylethylamine (DIPEA) or triethylamine.

- Alternatively, a compound having formula (II) is reacted in a so-called amidation reaction with a compound having formula $\text{R}_3\text{R}_4\text{NH}$ wherein R_3 and R_4 have the meanings as described hereinabove to give a thiazole derivative having formula (I).
 25 Such amidation reactions can be promoted by the use of trimethylaluminum $\text{Al}(\text{CH}_3)_3$ (For more information on aluminum-mediated conversion of esters to amides, see: J. I. Levin, E. Turos, S. M. Weinreb, *Synth Commun.* (1982), 12, 989-993.)

- Alternatively, a compound having formula $\text{R}_3\text{R}_4\text{NH}$ can be reacted with a strong base, such as lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS), potassium hexamethyldisilazide (KHMDS) or sodium hexamethyldisilazide (NaHMDS) and the like to give in situ a compound having formula $\text{R}_3\text{R}_4\text{NLi}$, $\text{R}_3\text{R}_4\text{NK}$ or $\text{R}_3\text{R}_4\text{NNa}$, respectively, which can then be reacted with a compound having formula (II) to give a thiazole derivative having formula (I).

- 35 Alternatively, a compound having formula (I) wherein R_3 and R_4 represent a hydrogen atom can be reacted with a strong base, such as LDA, LiHMDS, NaH and the like, followed by a reaction with a compound L-R_4 wherein L represents a so-

called leaving group such as Br, Cl, I and the like, and R₄ represents a branched or unbranched C₁₋₁₀ alkyl group, cycloalkyl-alkyl group or a branched or unbranched C₃₋₁₀ alkenyl group, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms.

Example I

Part A: Magnesium (3.04 gram, 0.125 mol) is suspended in anhydrous diethyl ether (500 mL) under a nitrogen atmosphere and an iodine crystal is added. A solution of 4-chlorobenzyl chloride (20.12 gram, 0.125 mol) in anhydrous diethyl ether (100 mL) is slowly added to maintain a gentle reflux. After cooling the resulting mixture to room temperature a solution of 2,4-dichlorobenzonitrile (17.2 gram, 0.10 mol) in toluene (100 mL) is slowly added. Temperature is raised to 135 °C and the diethyl ether is removed by distillation, toluene is added and the resulting mixture is refluxed for two additional hours. After cooling to room temperature a solution of HCl (1N, 400 mL) is slowly added under cooling and stirring. The resulting mixture is extracted twice with diethyl ether, dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography (dichloromethane) gives 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone as a yellow oil (19.96 gram, 67 % yield). Crystallisation from cyclohexane gives pure 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone. Melting point: 65-66 °C. ¹H-NMR (200 MHz, CDCl₃): δ 7.02-7.45 (m, 7H), 4.22 (s, 2H).

Part B: To a solution of 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (2.82 gram, 9.42 mmol) in benzene (25 mL) is added bromine (0.48 mL, 1.49 gram, 9.31 mmol) and the resulting solution is stirred at room temperature for two hours. Dichloromethane is added and the resulting solution is washed with aqueous NaHCO₃ solution. The organic layer is dried over MgSO₄, filtered and evaporated *in vacuo* to give 3.55 gram (quantitative yield) of 2-bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone as a yellow oil (purity ~ 95 % according to HPLC analysis). ¹H-NMR (200 MHz, CDCl₃): δ 7.00-7.50 (m, 7H), 6.16 (s, 1H).

Analogously was prepared:

2-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethanone. ¹H-NMR (200 MHz, CDCl₃): δ 7.95 (d, J = 8 Hz, 2H), 7.23-7.62 (m, 5H), 6.77 (s, 1H).

Part C: 2-Bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (9.83 gram, 26.0 mmol) and ethyl thiooxamate (5.28 gram, 39.6 mmol) are dissolved in absolute ethanol (50 mL). The resulting red solution is heated at reflux temperature for 4 hours. After evaporation *in vacuo* the crude red material (14 gram) is suspended in a mixture of dichloromethane and methyl-tert-butyl ether. The formed solids are removed by filtration. The resulting filtrate is purified by column chromatography (eluant: dichloromethane: R_f ~0.4) to give ethyl-5-(4-chlorophenyl)-4-(2,4-

dichlorophenyl)thiazole-2-carboxylate as a yellow oil (5.21 gram, 48 % yield) which slowly solidifies. Melting point: 117-118 °C. ¹H-NMR (200 MHz, CDCl₃): δ 7.53, (d, J = 2 Hz, 1H), 7.40 (dt, J = 8 Hz, J = 2 Hz, 2H), 7.22-7.35 (m, 4H), 4.52 (q, J = 7 Hz, 2H), 1.45 (t, J = 7 Hz, 3H).

5 Analogously was prepared:

Ethyl-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylate.

Part D; Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.00 gram, 2.42 mmol) is added to 1-aminopiperidine (10 mL) and the resulting stirred mixture is heated at 50 °C for 4 hours. Dichloromethane is added and the resulting solution is washed twice with water, dried over MgSO₄, filtered and most of the dichloromethane is removed by evaporation *in vacuo*. Diisopropyl ether is added and the formed precipitate is removed by filtration. The filtrate is concentrated *in vacuo* and purified by flash chromatography (ethyl acetate: petroleum ether (40-60) = 1:3 (v/v)) to produce 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-(1-piperidinyl)thiazole-2-carboxamide (330 mg, 29 % yield) as a white foam. ¹H-NMR (400 MHz, CDCl₃): δ 7.92 (s, 1H), 7.47 (t, J = 2 Hz, 1H), 7.24-7.32 (m, 4H), 7.13 (dt, J = 8 Hz, J = 2 Hz, 2H), 2.85-2.93 (m, 4H), 1.40-1.82 (m, 6H).

Analogously were prepared:

- 20 4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-N-(1-piperidinyl)thiazole-2-carboxamide.
Melting point: 190-191 °C. ¹H-NMR (400 MHz, CDCl₃): δ 8.03 (s, 1H), 7.51 (d, J = 2 Hz, 1H), 7.22-7.38 (m, 6H), 2.90-2.97 (m, 4H), 1.75-1.84 (m, 4H), 1.44-1.52 (m, 2H).
- 5-(4-Chlorophenyl)-N-cycloheptyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide.
Melting point: 159-161 °C.
- 25 5-(4-Chlorophenyl)-N-cyclopentyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide.
Melting point: 111-113 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(trans-4-hydroxycyclohexyl)thiazole-2-carboxamide. Melting point: 109 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(2-methylcyclohexyl)thiazole-2-carboxamide. Melting point: 134-147 °C.
- 30 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(4-fluorobenzyl)thiazole-2-carboxamide.
Melting point: 142-144 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(trans-4-methylcyclohexyl)thiazole-2-carboxamide. Melting point: 165-166 °C.
- 35 5-(4-Chlorophenyl)-N-(cis-4-methylcyclohexyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide. Melting point: 72 °C.

Example 2

- 40 **Part A;** Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (4.10 gram, 9.93 mmol) is suspended in methanol (75 mL). A solution of KOH (1.98 gram, 30 mmol) in water (75 mL) is added and the resulting mixture is heated at reflux

temperature for 2 hours. The resulting yellow solution is allowed to attain room temperature, poured into water and acidified with 1N aqueous HCl to give a white precipitate. This precipitate is collected by filtration and twice washed with water. Drying *in vacuo* gives 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid as a white solid (2.59 gram, 68 % yield). ¹H-NMR (200 MHz, DMSO-d₆): δ 9.25 (s, 1H), 7.65-7.72 (m, 1H), 7.28-7.52 (m, 6H).

Analogously was prepared:

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid

- 10 **Part B;** 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (1.00 gram, 2.6 mmol) is suspended in anhydrous acetonitrile (20 mL) under a nitrogen atmosphere at room temperature. Diisopropylethylamine (DIPEA) (1.36 mL, 7.8 mmol), O-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate (HBTU) (1.08 gram, 2.85 mmol) and O-*tert*-butylhydroxylamine.HCl (0.35 gram, 25.1 mmol) are successively added and the resulting mixture is stirred overnight at room temperature. The resulting mixture is concentrated *in vacuo* and dichloromethane is added. The resulting solution is successively washed with water and brine, dried over MgSO₄, filtered and evaporated *in vacuo*. Subsequent flash chromatography (ethyl acetate:petroleum ether (40-60) = 1:3 (v/v)) gives N-(*t*-butoxy)-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (0.60 gram, 51 % yield) as a white foam. ¹H-NMR (400 MHz, CDCl₃): δ 9.20 (s, 1H), 7.47 (t, J = 2 Hz, 1H), 7.25-7.31 (m, 4H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 1.36 (s, 9H).

Analogously were prepared:

N-(*t*-Butoxy)-4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxamide. ¹H-NMR (400 MHz, CDCl₃): δ 9.23 (s, 1H), 7.52 (d, J = 2 Hz, 1H), 7.35 (dt, J = 8 Hz, J = 2 Hz, 2H) 7.23-7.31 (m, 4H), 1.40 (s, 9H).

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(*n*-pentyl)thiazole-2-carboxamide

¹H-NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.21-7.32 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 3.42-3.48 (m, 2H), 1.59-1.67 (m, 2H), 1.30-1.40 (m, 4H), 0.90 (t, J = 7 Hz, 3H).

5-(4-Chlorophenyl)-N-cyclohexyl-4-(2,4-dichlorophenyl)thiazole-2-carboxamide

¹H-NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.24-7.35 (m, 4H), 7.05-7.17 (m, 3H), 3.90-4.00 (m, 1H), 1.98-2.07 (m, 2H), 1.72-1.82 (m, 2H), 1.14-1.70 (m, 6H).

35 Example 3

- 40 **Part A;** To 4-bromobenzaldehyde (25 gram, 0.135 mol) is successively added 2,4-dichlorophenylacetic acid (27.7 gram, 0.135 mol), acetic anhydride (100 mL) and triethylamine (19 mL, 0.136 mol) and the resulting mixture is heated at reflux temperature for 90 minutes. The reaction mixture is cooled to 110 °C and water (100 mL) is slowly added. The resulting mixture is allowed to attain room temperature and ethyl acetate is added. The ethyl acetate layer is twice washed with water, dried over

MgSO₄, filtered and concentrated *in vacuo*. The resulting oil is crystallised from diisopropyl ether to give 3-(4-bromophenyl)-2-(2,4-dichlorophenyl)acrylic acid as a white solid (26.55 gram, 53 % yield).

- 5 **Part B:** 3-(4-Bromophenyl)-2-(2,4-dichlorophenyl)acrylic acid (26.55 gram, 71 mmol) is dissolved in anhydrous toluene (130 mL) and the resulting solution is cooled to 0 °C. Triethylamine (7.40 gram, 73 mmol) and diphenylphosphoryl azide (19.8 gram, 72 mmol) are successively added and the resulting mixture is stirred at 0 °C for 20 minutes and 150 minutes at room temperature. The reaction mixture is poured into
- 10 water and extracted three times with diethyl ether. The collected organic layers are dried over MgSO₄ and the diethyl ether is removed *in vacuo*. The resulting toluene layer is slowly added to refluxing toluene (150 mL). t-Butanol is added after 90 minutes and heating at reflux temperature is continued for 1 hour, followed by slow addition of concentrated hydrochloric acid (5 mL). After stirring the resulting solution
- 15 overnight at 90 °C it is allowed to attain room temperature, washed twice with water, dried over MgSO₄, filtered and evaporated *in vacuo* to give a yellow oil. This oil is crystallised from n-hexane to give 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (14.72 gram, 60 % yield). Melting point: 69-70 °C.

- 20 **Part C:** To a solution of 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (5.00 gram, 15 mmol) in benzene (50 mL) is dropwise added bromine (0.75 mL, 15 mmol) and the resulting solution is stirred for 4 hours at room temperature and concentrated *in vacuo*. Dichloromethane is added and the resulting solution is washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give 2-bromo-2-(4-
- 25 bromophenyl)-1-(2,4-dichlorophenyl)ethanone as an oil (5.96 gram, 94 % yield).

- Part D:** A solution containing 2-bromo-2-(4-bromophenyl)-1-(2,4-dichlorophenyl)ethanone (5.96 gram, 14 mmol) and ethyl thiooxamate (2.80 gram, 21 mmol) in ethanol (30 mL) is heated at reflux temperature for four hours. After cooling
- 30 to room temperature the precipitated crystalline material is removed by filtration. The filtrate is concentrated *in vacuo* and the resulting material (7.56 gram orange oil) is purified by flash chromatography (ethyl acetate/petroleum ether = 1/3 (v/v)) and subsequently crystallised from diisopropyl ether to afford ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl) thiazole-2-carboxylate (2.11 gram, 33 % yield). Melting point:
- 35 129-130 °C.

- Part E:** A stirred mixture containing ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.00 gram, 2.2 mmol) and 1-aminopiperidine (10 mL) is heated overnight at 50 °C. The resulting mixture is allowed to attain room
- 40 temperature, dichloromethane is added and the resulting solution is twice washed with water, dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil. Flash chromatographic purification of this oil (ethyl acetate/petroleum ether = 1/3 (v/v))

gives 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-N-(1-piperidiny)thiazole-2-carboxamide (870 mg, 78 % yield). Melting point: 171-173 °C.

Analogously were prepared:

- 5 4-(2,4-Dichlorophenyl)-N-(1-piperidiny)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 181-183 °C.
- N-Cyclohexyl-4-(2,4-dichlorophenyl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 140-142 °C.
- 4-(2,4-Dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 184-185 °C.
- 10 4-(2,4-Dichlorophenyl)-N-(4-morpholinyl)-5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxamide. Melting point: 95 °C.

Example 4

- 15 **Part A:** Ethyl 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.80 gram, 3.94 mmol) is dissolved in methanol (20 mL) and a solution of KOH (0.65 gram (85 %), 9.85 mmol) in water (20 mL) is added. The resulting mixture is heated at reflux temperature for 1 hour, poured into water and acidified with hydrochloric acid (1N solution). The formed precipitated material is collected by filtration and dried *in vacuo* at room temperature to give a quantitative yield of 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-thiazole-2-carboxylic acid. Melting point: 94-95 °C.

- Part B:** 5-(4-Bromophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (0.50 gram, 1.17 mmol) and diisopropylethylamine (DIPEA) (1.02 mL, 5.85 mmol) are dissolved in dichloromethane (5 mL) and cooled to 0 °C. 7-Aza-1-hydroxybenzotriazole (HOAt) (0.11 gram, 0.81 mmol) and 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (CIP) (0.50 gram, 1.76 mmol) are added, followed by addition of n-pentylamine (0.15 gram, 1.76 mmol) and the resulting mixture is stirred at room temperature overnight. Flash chromatographic purification (dichloromethane) gives 5-(4-bromophenyl)-4-(2,4-dichlorophenyl)-N-(n-pentyl)thiazole-2-carboxamide as an amorphous solid (0.28 gram, 48 % yield).

Analogously were prepared:

- 5-(4-Bromophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydro(1H)azepin-1-yl)thiazole-2-carboxamide. Melting point: 206-207 °C.
- 35 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(morpholin-4-yl)thiazole-2-carboxamide. Amorphous solid.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)thiazole-2-carboxamide. Melting point: 179-181 °C.

- 40 Example 5

- Part A:** To a solution of 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (0.50 gram, 1.30 mmol) in dichloromethane (10 mL) is successively added 1-aminohexahydro(1H)azepine (0.15 gram, 1.30 mmol), 7-aza-1-hydroxybenzotriazole (0.18 gram, 1.30 mmol), 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) (0.68 gram, 1.30 mmol) and diisopropylethylamine (0.34 mL, 1.95 mmol) and the resulting solution is stirred for 1 hour at room temperature. Concentration *in vacuo* gives a crude oil (2.01 gram) which is purified by flash chromatography (ethyl acetate/petroleum ether = 1/3 (v/v)) to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydro(1H)azepin-1-yl)thiazole-2-carboxamide (0.350 gram, 56 % yield). Melting point: 185-186 °C (after recrystallisation from diisopropyl ether).
- Analogously were prepared:
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(hexahydrocyclopenta-[c]pyrrol-2(1H)-yl)thiazole-2-carboxamide. Melting point: 173-174 °C.
- 15 N-Benzyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-methyl-thiazole-2-carboxamide. Melting point: 141-144 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(4-(trifluoromethyl)benzyl) thiazole-2-carboxamide. Melting point: 174-176 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)thiazole-2-carboxamide. Melting point: 194-195 °C.
- 20 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(endo-bicyclo[2.2.1]hept-2-yl)thiazole -2-carboxamide. Melting point: 181-183 °C.
- 4-(2,5-Dichlorophenyl)-N-(exo-bicyclo[2.2.1]hept-2-yl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 170 °C.
- 25 N-(Cyclohexyl)-4-(2,5-dichlorophenyl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 75 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(tetrahydro-2H-pyran-2-yloxy)thiazole -2-carboxamide. Melting point: 85 °C.
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(5,5,5-trifluoropentyl)thiazole-2-carboxamide. ¹H-NMR (400 MHz, CDCl₃): δ 7.47 (br s, 1H), 7.24-7.31 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 3.49 (q, J = 7 Hz, 2H), 2.07-2.20 (m, 2H), 1.62-1.77 (m, 4H).
- 30 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(2-fluoroethyl)thiazole-2-carboxamide. Amorphous solid. ¹H-NMR (400 MHz, CDCl₃): δ 7.52-7.58 (m, 1H), 7.47 (br s, 1H), 7.24-7.32 (m, 4H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.61 (dt, J = 47 Hz, J = 5 Hz, 2H), 3.72-3.84 (m, 2H).
- 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-N-(5-fluoropentyl)thiazole-2-carboxamide. ¹H-NMR (400 MHz, CDCl₃): δ 7.47 (br s, 1H), 7.24-7.30 (m, 5H), 7.14 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.45 (dt, J = 47 Hz, J = 6 Hz, 2H), 3.45-3.51 (m, 2H), 1.64-1.82 (m, 4H), 1.48-1.56 (m, 2H).
- 40 4-(2,5-Dichlorophenyl)-N-(4-morpholinyl)-5-(phenyl)thiazole-2-carboxamide. Melting point: 155-157 °C.

Example 6

- 5 Ethyl-5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.65 gram, 4.0 mmol) is dissolved in anhydrous THF (25 mL) and aniline (0.37 mL, 4.0 mmol) is added. The resulting solution is cooled to 0 °C and sodium hexamethyldisilazide (4.4 mL of a 1M solution in THF) is added. The reaction mixture is stirred for 2 hours. Water is added and the mixture is extracted twice with ethyl acetate. The combined
10 organic layer is washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue is crystallised from diisopropyl ether to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-N-phenyl-thiazole-2-carboxamide (1.42 g, 77 % yield). Melting point: 167-168 °C.

15 Example 7

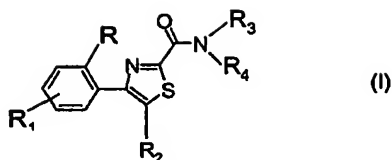
- Part A: Gaseous NH₃ is led through a stirred solution of ethyl 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylate (1.65 gram, 4.0 mmol) in methanol (25 mL) at room temperature. A small piece of sodium metal is added. After stirring the
20 resulting mixture for three hours the precipitate is collected by filtration, washed with a small portion of methanol and dried to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (1.16 gram, 76 % yield), melting point 195-198 °C. ¹H-NMR (200 MHz, CDCl₃): δ 7.48 (br s, 1H), 7.22-7.35 (m, 4H), 7.05-7.20 (m, 3H) 5.55-5.65 (M, 1H).

- 25 Part B: To a cooled (0 °C) stirred solution of 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxamide (1.16 gram, 3.02 mmol) in anhydrous DMF (20 mL) is added NaH (0.13 gram of a 60 % dispersion) in a nitrogen atmosphere. The resulting mixture is stirred for 1 hour and excess 4,4,4-trifluoro-1-bromobutane
30 (0.7 mL) is added. The resulting solution is stirred at room temperature for 1 hour, poured onto ice/water and extracted twice with diethyl ether. The collected diethyl ether layers are twice washed with water, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue is further purified by column chromatography (silica gel: eluant: dichloromethane) to give 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-
35 N-(4,4,4-trifluorobutyl)thiazole-2-carboxamide. Melting point: 99-101 °C.

Claims

1. A compound of formula (I)

5



wherein

- 10 – R represents a hydrogen atom or a substituent X from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl(C₁₋₃)sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl(C₁₋₃) aminosulfonyl,

15 branched or unbranched monoalkyl(C₁₋₃)-aminosulfonyl and acetyl,

 - R₁ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,
 - R₂ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning

20 or R₂ represents naphthyl,
 - R₃ represents a hydrogen atom or a branched or unbranched C₁₋₁₀ alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy,

25 halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkylsulfonyl, dimethylsulfamido, branched or unbranched C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R₃ represents a pyridyl or thienyl group,
 - 30 – R₄ represents branched or unbranched C₁₋₁₀ alkyl or cycloalkyl-alkyl group, branched or unbranched C₁₋₁₀ alkoxy, C₃₋₈ cycloalkyl, C₅₋₁₀ bicycloalkyl, C₆₋₁₀ tricycloalkyl, branched or unbranched C₃₋₁₀ alkenyl, C₅₋₈ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl

35 group or 1-3 fluoro atoms, or R₄ represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or R₄ represents a pyridyl or thienyl group, or R₄ represents a group NR₅R₆ wherein

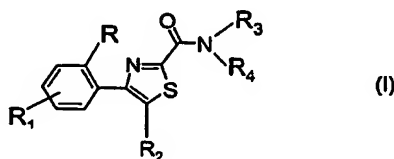
5 R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

10 - R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom,

and pro-drugs, stereoisomers and salts thereof.

15

2. A compound of formula (I)



20 wherein

- R represents a substituent Y from the group branched or unbranched C_{1-3} -alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido,

25 branched or unbranched (C_{1-3})-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl,
- R_1 represents hydrogen or one or more substituents Y, wherein Y has the above mentioned meaning.
- R_2 represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or R_2 represents naphthyl,

30
- R_3 is hydrogen,
- R_4 represents branched or unbranched C_{1-10} alkyl or alkyl-cycloalkyl, branched or unbranched C_{1-10} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl,

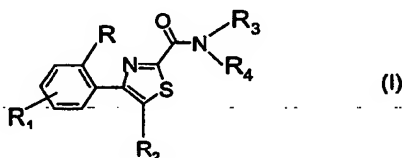
35 branched or unbranched C_{3-10} alkenyl, C_{5-8} cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may optionally be substituted with a hydroxy group, 1-3 methyl groups or an ethyl group or 1-3 fluoro atoms, or R_4 represents a benzyl or phenethyl group which

aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkylsulfonyl, dimethylsulfamido, branched or unbranched C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R₄ represents a pyridyl or thienyl group, or R₄ represents a group NR₅R₆ wherein

R₅ and R₆ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C₁₋₃ alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

3. A compound of formula (I)



wherein

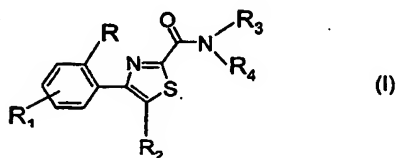
- R represents a substituent Y from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl,
- R₁ represents one or more substituents Y, wherein Y has the above mentioned meaning,
- R₂ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or R₂ represents naphthyl,
- R₃ is hydrogen,
- R₄ represents branched or unbranched C₁₋₁₀ alkyl or alkyl-cycloalkyl, branched or unbranched C₁₋₁₀ alkoxy, C₃₋₈ cycloalkyl, C₅₋₁₀ bicycloalkyl, C₆₋₁₀ tricycloalkyl, branched or unbranched C₃₋₁₀ alkenyl, C₅₋₈ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may

optionally be substituted with a hydroxy group, 1-3 methyl groups or an ethyl group or 1-3 fluoro atoms, or R_4 represents a benzyl or phenethyl group which aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched C_{1-3} -alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, branched or unbranched (C_{1-3})-alkylsulfonyl, dimethylsulfamido, branched or unbranched C_{1-3} -alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein, R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

20

4. A compound of formula (I)



25

wherein

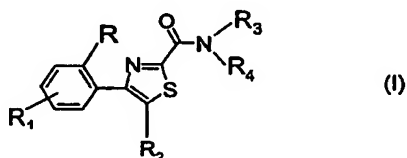
- R represents a halogen atom
- R_1 represents one or more substituents Y, wherein Y has the meaning as given in claim 2,
- 30 - R_2 represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or R_2 represents naphthyl,
- R_3 is hydrogen,
- R_4 represents branched or unbranched C_{1-10} alkyl or alkyl-cycloalkyl, branched or unbranched C_{1-10} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, branched or unbranched C_{3-10} alkenyl, C_{5-8} cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may optionally be substituted with a hydroxy group, 1-3 methyl groups or an ethyl

35

- group or 1-3 fluoro atoms, or R_4 represents a benzyl or phenethyl group which aromatic rings may be substituted with one or more substituents Z, which can be the same or different, from the group branched or unbranched C_{1-3} -alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, branched or unbranched (C_{1-3})-alkylsulfonyl, dimethylsulfamido, branched or unbranched C_{1-3} -alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein,
- R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

5. A compound of formula (I)



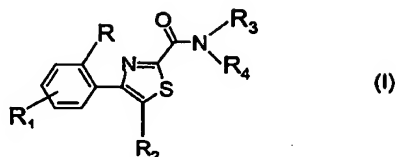
wherein

- R represents a halogen atom
- R_1 represents one or more substituents Y, wherein Y has the meaning as given in claim 2,
- R_2 represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the above mentioned meaning, or R_2 represents naphthyl,
- R_3 is hydrogen,
- R_4 represents a group NR_5R_6 wherein,
 R_5 and R_6 together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C_{1-3} alkyl, hydroxy or trifluoromethyl group or a fluoro atom

and pro-drugs, stereoisomers and salts thereof.

6. A compound of formula (I)

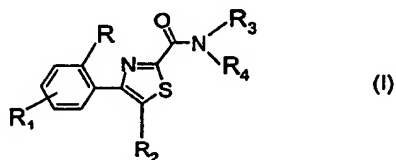
5



wherein

- 10 – R represents a halogen atom,
 – R₁ represents one or more halogen atoms,
 – R₂ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with one or more substituents Y, wherein Y has the meaning as given in claim 2, or R₂ represents naphthyl,
 15 – R₃ is hydrogen,
 – R₄ represents a group NR₅R₆ wherein,
 R₅ and R₆ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a
 20 branched or unbranched C₁₋₃ alkyl, hydroxy or trifluoromethyl group or a fluoro atom,
 and pro-drugs, stereoisomers and salts thereof.

25 7. Use of a compound of formula (I)



wherein

- 30 – R represents a hydrogen atom or a substituent X from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched alkyl(C₁₋₃)sulfonyl,

carboxyl, cyano, carbamoyl, branched or unbranched dialkyl(C₁₋₃) aminosulfonyl, branched or unbranched monoalkyl(C₁₋₃)-aminosulfonyl and acetyl,

- R₁ is a hydrogen atom or represents 1-4 substituents X, wherein X has the abovementioned meaning,

5 - R₂ represents a phenyl, thienyl, pyridyl or pyrimidinyl group, which groups may be substituted with 1-4 substituents X, wherein X has the abovementioned meaning or R₂ represents naphthyl,

- R₃ represents a hydrogen atom or a branched or unbranched C₁₋₁₀ alkyl or cycloalkyl-alkyl group or a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group branched or unbranched C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkylsulfonyl, dimethylsulfamido, branched or unbranched C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R₃ represents a pyridyl or thienyl group,

- R₄ represents branched or unbranched C₁₋₁₀ alkyl or cycloalkyl-alkyl group, branched or unbranched C₁₋₁₀ alkoxy, C₃₋₈ cycloalkyl, C₅₋₁₀ bicycloalkyl, C₆₋₁₀ tricycloalkyl, branched or unbranched C₃₋₁₀ alkenyl, C₅₋₈ cycloalkenyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R₄ represents a phenyl, benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, wherein Z has the abovementioned meaning, or R₄ represents a pyridyl or thienyl group, or R₄ represents a group NR₅R₆ wherein

R₅ and R₆ together with the nitrogen atom to which they are attached form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C₁₋₃ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, or

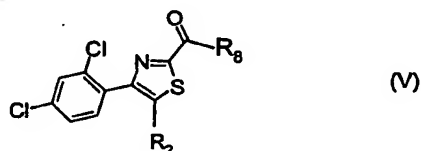
- R₃ and R₄ - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or unbranched C₁₋₃ alkyl, hydroxy or trifluoromethyl group or a fluoro atom, and pro-drugs, stereoisomers and salts thereof,

for the preparation of a pharmaceutical composition for the treatment of disorders involving CB₁ cannabinoid neurotransmission such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle

spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, plaque sclerosis, viral encephalitis, demyelination related disorders and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders

8. A pharmaceutical composition containing at least one compound as claimed in one of the claims 1-7 as an active component.

9. A compound of formula (V)



wherein R_2 has the meaning as given in claim 1 and R_8 represents a hydroxy group, a branched or unbranched alkoxy (C_{1-4}) group, a benzyloxy group or a chloro atom.

10. Use of a compound as claimed in one of the claims 1-7 for the preparation of a pharmaceutical composition for the treatment of disorders involving CB_1 cannabinoid neurotransmission such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, plaque sclerosis, viral encephalitis, demyelination related disorders and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50063

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/68 A61K31/425 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 46209 A (SANOFI SYNTHELABO ;BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN) 10 August 2000 (2000-08-10) claims; examples	1-10
A	PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, August 1999 (1999-08), pages 635-664, XP000923352 ISSN: 0929-8673 page 641 -page 657; figure 5	1-10
A	US 5 624 941 A (BARTH FRANCIS ET AL) 29 April 1997 (1997-04-29) claims; examples	1-10
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

16 June 2003

Date of mailing of the international search report

25/06/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Menegaki, F

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50063

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 01 66540 A (GAIBA ALESSANDRA ;SMITHKLINE BEECHAM PLC (GB); TAKLE ANDREW KENNET) 13 September 2001 (2001-09-13) claims</p> <p>-----</p>	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50063

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0046209	A	10-08-2000	FR 2789078 A1	04-08-2000
			FR 2789079 A1	04-08-2000
			AU 754771 B2	21-11-2002
			AU 2298900 A	25-08-2000
			BG 105749 A	28-02-2002
			BR 0007895 A	30-10-2001
			CA 2358885 A1	10-08-2000
			CN 1346349 T	24-04-2002
			CZ 20012697 A3	17-10-2001
			EE 200100399 A	15-10-2002
			EP 1150961 A1	07-11-2001
			WO 0046209 A1	10-08-2000
			HR 20010564 A1	31-08-2002
			HU 0201278 A2	28-12-2002
			JP 2002536366 T	29-10-2002
			NO 20013736 A	28-09-2001
			NZ 512886 A	25-10-2002
			PL 350030 A1	21-10-2002
			SK 10872001 A3	03-12-2001
			TR 200102054 T2	21-05-2002
			US 2002188007 A1	12-12-2002
			US 6432984 B1	13-08-2002
US 5624941	A	29-04-1997	FR 2692575 A1	24-12-1993
			FR 2713224 A1	09-06-1995
			FR 2713225 A1	09-06-1995
			AT 149489 T	15-03-1997
			AU 4143893 A	06-01-1994
			BR 1100409 A3	13-10-1999
			BR 9302435 A	11-01-1994
			CA 2098944 A1	24-12-1993
			CZ 9301172 A3	16-03-1994
			DE 69308395 D1	10-04-1997
			DK 576357 T3	15-09-1997
			EP 0576357 A1	29-12-1993
			ES 2101258 T3	01-07-1997
			FI 932891 A	24-12-1993
			GR 3023535 T3	29-08-1997
			HU 64526 A2	28-01-1994
			IL 106099 A	15-07-1998
			JP 3238801 B2	17-12-2001
			JP 6073014 A	15-03-1994
			MX 9303664 A1	31-01-1994
			NO 932296 A	27-12-1993
			NZ 247961 A	28-08-1995
			RU 2119917 C1	10-10-1998
			SK 65493 A3	02-02-1994
			TW 494096 B	11-07-2002
			ZA 9304511 A	22-02-1994
			AT 154012 T	15-06-1997
			AU 685518 B2	22-01-1998
			AU 7899994 A	15-06-1995
			BR 1100984 A3	14-03-2000
			CA 2136893 A1	21-06-1995
			CN 1110968 A ,B	01-11-1995
			CZ 9403016 A3	14-06-1995
			DE 69403614 D1	10-07-1997
			DE 69403614 T2	22-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50063

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5624941	A	DK 656354 T3	29-12-1997
		EP 0656354 A1	07-06-1995
		ES 2105575 T3	16-10-1997
		FI 945690 A	03-06-1995
		GR 3024470 T3	28-11-1997
		HK 1000599 A1	09-04-1998
		HU 71498 A2	28-11-1995
		IL 111719 A	28-10-1999
		JP 3137222 B2	19-02-2001
		JP 7309841 A	28-11-1995
		JP 2001026541 A	30-01-2001
		NO 944625 A	06-06-1995
		NZ 270025 A	26-09-1995
		PL 306067 A1	12-06-1995
		RU 2141479 C1	20-11-1999
WO 0166540	A	13-09-2001	
		AU 3584401 A	17-09-2001
		EP 1261602 A1	04-12-2002
		WO 0166540 A1	13-09-2001

THIS PAGE BLANK (USPTO)